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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/645,706	08/24/2000	Keith V. Wood	341.005US1	3329

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EXAMINER
PROUTY, REBECCA E

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/645,706	Applicant(s) Wood et al.
	Examiner Rebecca Prouty	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 18, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above, claim(s) *10, 13, 16, 17, 19, 22, 23, 40, 46, 48-53, 55-59,* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-9, 11, 12, 14, 15, 18, 20, 21, 24-39, 41-45, 47, 54, and 60-63* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election with traverse of Group I, claims 1-45, 47, 54 and 60-64 and the species of SEQ ID NO:9 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the inventions are so closely related within the context of the disclosure that they cannot be considered to be independent and distinct and as no additional burden of search would be present for the search of all groups as all claims are within the same class (435). This is not found persuasive because while the inventions of groups I and III are clearly related as product and process of making, this was admitted in the restriction requirement. 35 U.S.C. 121 does not preclude restriction of inventions related as product and process of making and MPEP 806.05(f) clearly shows that restriction between may be made where either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process. In the instant case the product can be made by chemical synthesis. The claims of Groups I and II are related in that the nucleic acids of Group I encode the proteins of Group II, but they are patentable distinct compounds for the reasons previously presented. Finally the classification of the claims of all three groups within the same class is not evidence of the lack of a additional burden of

search as each of the three groups are present in distinct subclasses within this class. Class 435 of the US patent classification system is an enormous class with hundreds of subclasses many with several thousand documents each and a total number of documents in the tens of thousands. As such a substantial additional burden would be present for the coexamination of all claims.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10, 13, 16, 17, 19, 22, 23, 40, 46, 48-53, 55-59, and 64-66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claim 54 is objected to as depending from non-elected claims.

Claims 1-9, 11, 12, 14, 15, 18, 20, 21, 24-39, 41-45, 47, 54 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (from which claims 2-9, 11, 12, 14, 15, 18, 20, 21, 24-39, and 41-45 depend) and non-elected claim 49, from which elected claim 54 depends are vague and indefinite in the recitation of "3-fold fewer transcription regulatory sequences relative to the average number of such sequences resulting from random selections of codons at the codons which differ" as the specification provides no method for determining the average number of such sequences resulting from random selections of codons at the codons which differ. Without knowing all the possible sequences which are considered to be "transcriptional regulatory sequences" such a calculation is impossible as one could never obtain a count of the number of such sequence in any reference nucleic acid. Even if such information were disclosed (which it is not) this calculation would appear to be extremely difficult and time consuming and would require a extraordinary knowledge of statistics above and beyond that of the ordinary artisan in the field of genetic engineering. Since the specification teaches no method of making this calculation, or even a rough estimate thereof, for the purposes of examination, this limitation has been interpreted as "at least 3 fewer transcription regulatory sequences relative to the parent nucleic acid". Claim 63 is similarly confusing in the recitation of 3-fold fewer transcriptional regulatory sequences relative to a

vector comprising a parent nucleic acid sequence" as without knowing all the possible sequences which are considered to be "transcriptional regulatory sequences" such a calculation is impossible as one could never obtain a count of the number of such sequence in the parent nucleic acid.

Claim 45 is confusing in the recitation of "A reporter gene expression kit comprising..." as the expression vector recited does not necessarily encode a reporter gene.

Claim 47 is indefinite in the recitation of "stringent conditions" as the specification does not define what conditions constitute "stringent". While pages 20-21 of the specification describe conditions which are intended to be "high stringency", "medium stringency" and "low stringency", it is not which of these definitions are included within the term "stringent" and in the art what is considered stringent varies widely depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of a gene encoding SEQ ID NO:9, a sequence must be to be included within the scope of these claims.

Claims 1-6, 14, 15, 20-21, 24-33, 35-39, 41-45, 47, 54, 60, 61 and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of variant DNA molecules encoding a polypeptide having at least 85% identity to a wild type polypeptide and having more than 25% of the codons altered and having at least 3 fewer transcription regulatory sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9.

The specification does not contain any disclosure of the function of all nucleic acids within the scope of the claimed genera. The genera of nucleic acids that comprise these above nucleic acids are large and variable with the potentiality of encoding many different proteins. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims. The specification discloses only a few species of the claimed genera which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C.

112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-6, 14, 15, 20-21, 24-33, 35-39, 41-45, 47, 54, 60, 61 and 63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a variant of a parent DNA molecule encoding a polypeptide identical to a polypeptide encoded by said parent DNA and having more than 25% of the codons altered and having at least 3 fewer transcription regulatory sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9 under high stringency conditions and encoding a polypeptide having luciferase activity, does not reasonably provide enablement for any variant DNA molecules encoding a polypeptide having at least 85% identity to a wild type polypeptide and having more than 25% of the codons altered and having at least 3 fewer transcription regulatory sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim are so broad as to encompass any variant DNA molecules encoding a polypeptide having at least 85% identity to a wild type polypeptide and having more than 25% of the codons altered

and having at least 3 fewer transcription regulatory sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variant nucleic acids broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to modifying the nucleic acid sequence of a desired gene without changing the encoded protein sequence.

While recombinant and mutagenesis techniques are known, it is <u>not</u> routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is

unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any variant DNA molecules encoding a polypeptide having at least 85% identity to a wild type polypeptide and having more than 25% of the codons altered and having at least 3 fewer transcription regulatory sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9 because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of any protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the

scope of the claims broadly including any variant DNA molecules encoding a polypeptide having at least 85% identity to a wild type polypeptide and having more than 25% of the codons altered and having at least 3 fewer transcription regulatory sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of variant nucleic acids having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6, 34-37, 44, 54, and 60-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Iannacone et al.

Iannacone et al. teach a modified *cry*3B gene in which 44% of the codons have been altered without altering the protein coding

sequence such that the altered sequences were designed to optimize the codon selection for plant host cells and eliminate sequences which would destabilize the mRNA including polyadenylation sequences and splicing sites. The altered gene includes at least 6 fewer polyadenylation sequences and was inserted into a plant expression vector including a Kozak consensus sequence preceding the ATG initiation codon. The altered gene is transcribed and translated efficiently in transgenic plants while the wild type gene is not transcribed at all.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11, 12, 14, 15, 20, 21, 24-39, 41-45, 54, and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Sherf et al. (US Patent 5,670,356) in view of Zolotukhin et al. (US Patent 5,874,304) and Iannacone et al.

Sherf et al. teach a modified firefly luciferase gene in which 14% of the codons have been altered without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for human host cells and eliminate sequences which encode transcription factor binding sites for know mammalian transcription factors including ATF, AP1, Sp1, AP2 etc. which would interfere with its "genetically neutral" behavior expected of a reporter gene. The altered gene includes at least 6 fewer transcription factor binding sites and was inserted into several mammalian expression vectors. The altered gene is transcribed and translated efficiently in mammalian host cells. The altered luciferase differs from the variant nucleic acids of the claims in that 25% or more of the codons were not altered. Sherf et al. further disclose that similar modifications could be made to other luciferase genes including click beetle luciferase

Zolotukhin et al. teach a modified *Aequorea victoria* GFP gene in which 37% of the codons have been altered (and optionally

up to even 80-90% may be altered) without altering the protein coding sequence such that the altered sequences were designed to optimize the codon selection for human host cells. is inserted into an expression vector including a Kozak consensus sequence preceding the ATG initiation codon which optionally may include a multiple cloning site positioned between the promoter and the humanized GFP gene and/or downstream of the GFP gene. The altered gene preferably includes CTG codons encoding leucine, GTG or GTC codons encoding valine, GGC codons encoding glycine, ATC codons encoding isoleucine, CCT codons encoding proline, CGC codons encoding arginine, AGC codons encoding serine, ACC codons encoding threonine, and GGC or GGT codons encoding alanine and is transcribed and translated 5-10 times more efficiently in human cells than the wild type gene.

Iannacone et al. is discussed above and particularly teach the removal of sequences which would destabilize the mRNA encoding a desired gene during codon optimization in particular the removal of polyadenylation sequences and splicing sites.

Therefore, it would have been obvious to further modify the luciferase gene of Sherf et al. to both increase the codon preference for humans and to remove potential polyadenylation sites and splice sites in order to further increase its usefulness as a reporter gene in human and other mammalian cells.

One would have had a reasonable expectation of success in view of the results of Zolotukhin et al. and Iannacone et al. which both show that such alterations of other genes which are to be expressed in evolutionarily highly distinct organisms from those in which they evolved substantially improve the levels of expression in the new host.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Rebecca Prouty
Primary Examiner
Art Unit 1652